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Infective endocarditis

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Infective endocarditis (IE) is a non-contagious infection of intracardiac structures which usually affects the valves of the heart but, in contemporary practice, may also involve infection of indwelling cardiac devices. Patients occasionally present acutely with severe sepsis but most still manifest with a non-specific illness of insidious onset having been symptomatic for several weeks or months. IE remains a challenging disease because of its variable presentation and frequent difficulty in securing the diagnosis. Population-based studies are scarce, but US data indicate the incidence is currently 5–7/100,000 person years,[1] but slowly rising[2] as a result of:

- an ageing population who develop degenerative valve lesions
- the increasing number of patients who receive prosthetic heart valves and other implantable cardiac devices
- the rising number of patients who receive renal replacement therapy via long-term vascular access devices
- ongoing problems in intravenous (iv) drug users, and
- the expanding number of immunosuppressed patients.

IE can be classified in terms of the type of cardiac structure affected and the causative organism involved, since these two factors affect prognosis and the choice and duration of antimicrobial therapy. IE is mainly caused by bacteria, but fungi are occasionally implicated. Staphylococci are now the most common bacterial cause of IE worldwide, accounting for 42% of episodes, 31% of which are due to *Staphylococcus aureus*.[3] Accompanying this rise, there has been a proportionate reduction in the number of infections caused by oral streptococci (now 17% of cases). Enterococci are the third most frequent cause of IE and consistently account for approximately 10% of episodes.[3]

Further classification by type of cardiac structure divides IE into:

- native valve endocarditis
- prosthetic valve endocarditis, and
- cardiac device-related IE – most commonly affecting permanent pacemakers and implantable cardioverter-defibrillators.

Diagnostic methods

The essential diagnostic methods for IE are blood cultures and echocardiography. These investigations are needed to confirm continuing bacteraemia and to demonstrate vegetations and/or new paravalvular regurgitation of prosthetic valve(s). The synthesis of clinical and microbiological findings with echocardiographic appearances is now known as the Duke criteria, first published in 1994. The original algorithm has been modified and provides an objective framework to assist diagnosis (Table 1).[4,5] Definitions of positive echocardiographic findings in IE are provided in Table 2.

Transoesophageal echocardiography

The limitations of transthoracic echocardiography include reduced ability to detect vegetations less than 5 mm in size.[6] Conversely, the superior sensitivity and specificity of transoesophageal echocardiography (TOE) are well established. There should be a low threshold for this investigation if clinical suspicion is high and the transthoracic study is non-diagnostic. TOE should be used in all cases of suspected prosthetic valve endocarditis because the prosthesis itself generates acoustic shadows which limit the usefulness of transthoracic imaging. In addition, detection of valve dehiscence, perivalvular extension of infection, abscesses, fistulae and leaflet perforation are all more reliably detected using this technique.[7]

Blood culture-negative endocarditis

Depending on the patient group and type of structure affected, 5–12% of IE cases are blood culture-negative. Negative cultures are more frequent in prosthetic valve and cardiac device-related IE.[3] Contributing factors include the recent use of antibiotics, organisms that are difficult to culture and inadequate blood sampling. A novel technique in these cases is broad-range 16S ribosomal RNA gene polymerase chain reaction analysis of tissue taken at the time of valve surgery (where appropriate). The results can guide the appropriate choice of antimicrobial therapy. The technique is currently limited to patients undergoing valve surgery, but application to whole blood samples should soon be feasible.[8] Consideration should also be given to serological testing for *Bartonella*, *Brucella*, Q-Fever, *Mycoplasma* and *Legionella* species when blood cultures are negative.

Antimicrobial regimens

Knowledge of the causative organism in IE is key to the selection of appropriate antimicrobial therapy. Whether infection affects a native cardiac structure or an indwelling cardiac device also influences the choice and duration of treatment. Biofilm formation on medical devices (particularly by staphylococci) necessitates the use of combination therapy for many of these infections. Meticillin-susceptible *S. aureus* native valve infections can usually be cured with flucloxacillin monotherapy. Routine addition of gentamicin is no longer recommended because of toxicity and a lack of supporting evidence.[9] Meticillin-resistant *S. aureus* infection affecting both native and prosthetic valves is now widespread and can be very difficult to treat. For several decades, vancomycin has been the cornerstone of therapy in this setting, but low-level resistance to this agent is emerging

and has been associated with treatment failure. The new anti-Gram-positive agents, linezolid and daptomycin, may be useful. Daptomycin is licensed for use in right-sided *S. aureus* IE on the basis of non-inferiority to standard therapy in a single randomised controlled trial.[10]

Most oral streptococci remain susceptible to penicillin and high-dose iv therapy with benzylpenicillin is safe and effective. Addition of gentamicin is recommended for these bacteria during short-course treatment or for isolates with reduced susceptibility to penicillin.[9] Although enterococci are generally susceptible to penicillin, monotherapy is usually inadequate and additional gentamicin is recommended for some or all of the course of treatment.[11]

Complications and mortality

Heart failure is the most frequent complication of IE (50–60% of cases) and the most common indication for surgery. It is more likely to occur with infection of the aortic (29%) than the mitral valve (20%).[12] Embolic events occur in 20–50% of cases, with the highest risk in staphylococcal infection, if the mitral valve is involved and the vegetation is larger than 10 mm.[13] The risk of embolism falls significantly after two weeks of antimicrobial therapy. Cerebral embolism, causing either transient or permanent ischaemic damage, occurs in 20–40% of cases and is

Table 1. The modified Duke criteria used in the diagnosis of infective endocarditis (IE).

Major criteria		
Blood cultures positive for IE	1	Typical micro-organisms consistent with IE from two separate sets of blood cultures: • eg Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus OR* • Community-acquired enterococci (in the absence of a primary focus) *OR*
	2	Micro-organisms consistent with IE from persistently positive blood cultures: • at least 2 positive blood cultures taken >12 h apart *or* • all of 3 or a majority of >4 separate blood cultures (>1 hr between 1st and last samples) *OR*
	3	Single positive blood culture for *Coxiella burnetti* or phase 1 IgG antibody titre >1:800
Evidence of endocardial involvement	1	Typical echocardiographic features (Table 2)
	2	New valvular regurgitation
Minor criteria	1	Predisposing cardiac lesion, history of iv drug use
	2	Pyrexial illness with temperature >38°C
	3	Vascular phenomena: major arterial emboli, mycotic aneurysms, septic pulmonary emboli, Janeway lesions, conjunctival haemorrhages, intracranial haemorrhages
	4	Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
	5	Microbiological evidence: positive blood cultures not meeting criteria of a major finding, or serological evidence of active infection with organism consistent with IE
Diagnosis of IE:		**definite** with 2 major criteria *or* 1 major and 3 minor criteria *or* 5 minor criteria **possible** with 1 major and 1 minor criteria *or* 3 minor criteria

HACEK = *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikinella*, *Kingella*; Ig = immunoglobulin; iv = intravenous.

Table 2. Echocardiographic abnormalities in infective endocarditis.

Vegetations	**Oscillating or non-oscillating masses on valves or other endocardial structures, including implanted intracardiac materials**
Abscess	Circumscribed echodense or echolucent area at the base of a cardiac valve (may also occasionally be intramyocardial)
Dehiscence of a prosthetic valve	Paravalvular regurgitation, often associated with excessive movement (rocking) of the prosthesis
Perforation	Abnormal flow through a valve leaflet
Fistula	Abnormal communication between two cardiac chambers developed as a result of a perforation
Pseudoaneurysm	Perivalvular echo-free area with flow within which flow is detected with Doppler sampling
Valve aneurysm	Abnormal bulging of valvular tissue

associated with excess mortality. Urgent surgery is recommended unless there is coma or evidence of intracerebral haemorrhage. Splenic infarcts/abscesses and deep spinal infection are important complications and may cause persistent fever; presentation is often atypical and diagnosis may be difficult.

Indications for surgery

Case series demonstrate that 50% of patients with IE require surgery, either acutely or shortly after completing antimicrobial treatment.[12] Indications for surgery are:

- refractory heart failure
- uncontrolled infection (signalled by persistent fever after 7–10 days of appropriate antimicrobial treatment)
- risk of or recurrent embolism, and
- abscess formation.

The timing of surgery is considered on a case-by-case basis, but early involvement of a cardiac surgeon is of fundamental importance. The general condition of the patient is central to decision making and there is no basis for delaying surgery to allow prolonged administration of antibiotics to 'sterilise' the operating field. Contrary to previous reports, there is no evidence that bioprostheses are less susceptible to recurrent infection than metallic valves.[14]

The management of cardiac device-related IE is a new area and the best outcomes are achieved after close liaison between the cardiologist, cardiac surgeon and microbiologist. The most common pathogens are staphylococci (particularly *S. aureus* and *S. epidermidis*). Extraction of infected pacing and device systems is often necessary to affect a cure and usually accomplished without need for open-heart surgery. The surgical management of IE has been recently reviewed and is summarised in the European Society of Cardiology guidelines on the management of IE.[15]

Conclusions

Rarely does a patient with IE present with the classical physical signs described by Osler (eg Janeway lesions and Oslers nodes). A high degree of clinical suspicion is essential to make the diagnosis. The protean manifestations of IE mean that it can present to almost any medical specialty. High-risk groups, such as patients with artificial cardiac devices, those on haemodialysis and iv drug users are self-evident, but the disease may also affect individuals with no known cardiac abnormality.

Regular physical examination, supplemented by repeat echocardiography when necessary, forms the basis of monitoring during treatment.[16] The complexity of the chosen antimicrobial regimen and possible adverse effects of therapy mean that joint care between the physician-in-charge (ideally a cardiologist) and a microbiologist represents best practice. In most cases, this multidisciplinary approach should include a cardiac surgeon who is aware of the patient's case early in their illness. The mortality of the condition remains appreciable owing to the unpredictable risk of major complications of the disease, resistance to antimicrobial therapy and frequent affliction of high-risk patients (eg the elderly) who may be poor candidates for surgery.

Recent National Institute for Health and Clinical Excellence guidance revised long-standing recommendations on the role of antibiotic prophylaxis prior to invasive (notably dental) procedures in susceptible patients. This practice is no longer recommended and has been replaced by emphasis on good oral and cutaneous hygiene.[17] These changes and the general lack of reliable data on this infrequent but serious infection have prompted a call for a national UK registry to track its true incidence and outcome.

Key Points

Although still rare, the incidence of infective endocarditis is increasing and its epidemiology changing; mortality remains around 20%

Staphylococci have replaced streptococci as the most common pathogens

Routine antibiotic prophylaxis is no longer recommended

Echocardiography and blood cultures remain the cornerstones of diagnosis but new molecular-based methods are emerging as useful adjuncts

A multidisciplinary approach between cardiologist, microbiologist and cardiac surgeon is central to optimising patient outcome

KEY WORDS: arterial embolism, infective endocarditis, pacemaker infection, staphyloccal bacteraemia, valvular heart disease

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